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# Influence of proximity on the permeability enhancing effect of microcontainers for oral insulin delivery

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## Introduction

Permeation enhancers (PEs) are often used in the field of oral peptide delivery. The dilution effect caused by the large surface area of the small intestine might, however, decrease their effect. Microcontainers (MCs), capable of confining the absorptive area of peptide and PE by unidirectional release, could potentially help overcoming this issue, and have previously shown promising results in increasing absorption of small molecules.<sup>1</sup>

## Aim

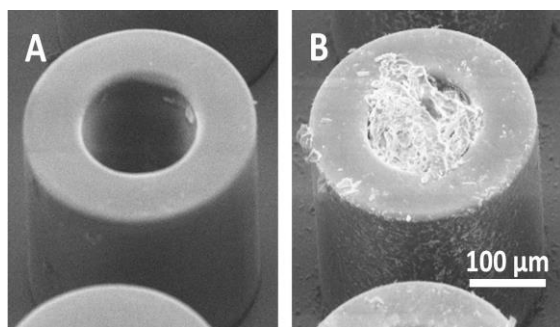
To validate the concept of increasing insulin permeability by confined co-localational release of insulin and PE, and to assess the influence of distance between the point of unidirectional release and the barrier.

## Method

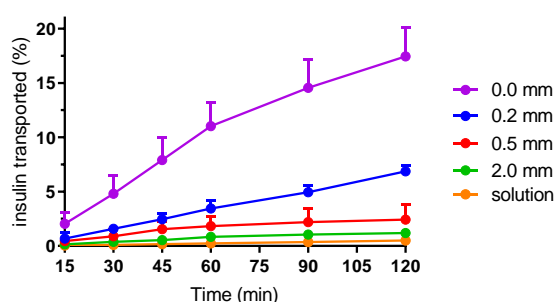
MCs, fabricated by photolithography in SU-8 on silicon chips, were filled with a powder mixture (1:1 w/w) of insulin and sodium caprate ( $C_{10}$ ) by centrifugal force (Fig 1). Insulin transport was monitored by HPLC-UV across Caco-2 monolayers in Transwells® with different distances (0-2 mm) between the cells and the chip holding 625 microcontainers. Collective directional release from the MCs towards the monolayer was ensured for all distances. A solution of 0.1 mM insulin and 3 mM  $C_{10}$  (1:1 w/w), equivalent to the amounts filled in MCs, was used as control group. A combination of TEER measurements and confocal laser scanning microscopy was used to evaluate the integrity of the monolayers.

## Results

Significant increases in insulin flux were achieved by release from all distances, compared to the solution of 0.1 mM insulin and 3 mM  $C_{10}$  (Fig 2). A drop in TEER value of 73 % was observed after release from microcontainers from 0.0 mm to the cells, and reversibility of this effect was evident upon 24 h subsequent incubation as an 86 % recovery of the initial TEER of the monolayer before the transport study. Confocal microscopy revealed local areas of cell damage after release from microcontainers from 0.0 and 0.2 mm, however, no monolayer deterioration was observed upon release from 0.5 and 2.0 mm.



**Figure 1:** Left: empty MC, Right: loaded MC



**Figure 2:** Transport profiles from MCs